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Original Article

The incidence of recurrence of tuberculosis and its related factors in smear-positive pulmonary tuberculosis patients in Iran: A retrospective cohort study

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ABSTRACT

Background and Aim: Studying the recurrence of smear-positive pulmonary tuberculosis (TB) is a convenient way to evaluate the effectiveness of TB control programs and identify vulnerable patients. In the present study, the rate of recurrence of TB and its predictors were determined in Iran. **Materials and Methods:** This study was a retrospective cohort. Eligible people were patients with smear-positive TB who were diagnosed from 2002 to 2011. The end of the follow-up time was December 2013. The number of people who entered the cohort was 1,271 subjects. In order to determine the predictors of recurrence, multivariate logistic regression was used. Analysis was done using SPSS 20. **Results:** The recurrence incidence was 8.3% and in 85.9% of these patients, it occurred in the time interval of 1-5 years after successful treatment. The recurrence rate was not significantly related to gender, age group, and diabetes. But it was significantly higher in patients whose sputum smear grading before treatment was 2 + or more, patients with positive sputum smear at the end of the second month of the treatment, patients who had completed treatment, and patients who were smokers ($P < 0.05$). **Conclusions:** Our study showed that a considerable percentage of smear-positive pulmonary TB patients experience recurrence and that some patients are at a higher risk of recurrence.

KEY WORDS: Incidence, recurrence, relapse, tuberculosis

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INTRODUCTION

Tuberculosis (TB) is one of the main health issues in many countries. This disease remains a major source of morbidity and mortality worldwide.[1-4] Recurrence of TB refers to a situation where a patient who has received at least 6 months of anti-TB drugs and whose smear or sputum culture was negative at the end of treatment develops active TB again after successful treatment.[5-7] If recurrent TB is the regrowth of *Mycobacterium tuberculosis* due to the same strain of previous TB episode, it is known as relapse. If recurrent TB is not due to the same strain of the previous TB episode, it is known as reinfection with a different *Mycobacterium tuberculosis* strain. Studies have indicated that the recurrence rates in countries with low or medium TB incidence are mainly due to relapse of the same strain of TB with which the patient was previously infected.[5,8,9]

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Among the studies conducted in different parts of the world, different recurrence rates have been reported. Vree *et al*. in Vietnam showed that 21 out of 244 (8.6%) patients experienced a recurrence of the disease 1-2 years after successful treatment.[10] A study in southern Ethiopia reported that 15 out of 368 (4.1%) smear-positive TB patients experienced a recurrence of the disease after successful treatment.[11] In another study carried out by Crofts *et al*. in England and Wales, the recurrence incidence was reported to be 4.1 in 1,000 person-years.[12]

The incidence of smear-positive TB in Iran was 6.9-7.6 per 100,000 people between 2005 and 2011. The incidence of smear-positive pulmonary TB in Mazandaran in 2009 was 4.3 per 100,000 people.[13,14] In a study carried out by Velayati *et al*. on multidrug resistant (MDR) TB patients, 23 out of 65 MDRTB patients (35%) experienced recurrence.[15]

Studying the recurrence of TB in patients is a convenient way to evaluate the effectiveness of TB control programs and identify patients with the highest vulnerability.[5,12] However, it seemed as if the documents and evidences related to this subject were inadequate in Iran. Therefore, in this study, the recurrence rate of TB after successful treatment and its predictors were determined in smear-positive TB patients in Mazandaran Province in the north of Iran.

MATERIALS AND METHODS

This study was a retrospective cohort study. The source of data was the TB register unit at the Ministry of Health and Medical Education, Shahrak-e-Gharb, Tehran, Iran. The patients followed up in this study were smear-positive TB patients with Iranian nationality who received a period of 6 months of treatment with anti-TB drugs and were recorded as treated (who were either cured or had completed treatment). These patients were diagnosed between 2002 and 2011. The end of follow-up was December 2013. The samples of 1,271 subjects were entered into the cohort.

In order to compare the demographic characteristics and variables studied between the relapse group and the group that did not have relapse, Chi-square test or Fisher's exact test was used for the categorical variables and independent *t*-test was used for the continuous normal variables. After univariate analysis in order to adjust for confounders, multivariate logistic regression was used. All the tests were two-sided and the significant level considered was less than 0.05. Analysis was done using SPSS 20 (SPSS Inc., Chicago IL).

The present project was approved by the Research Deputy of Kerman University of Medical Sciences (Code No. 92-136). The first and the last name of the patients were not recorded in the checklist and each patient was identified through a number.

RESULTS

The number of the patients followed up in this study was 1,271 and majority of them were males (56.2%). The mean age of all smear-positive pulmonary TB patients in the cohort was 48.4 ± 20.7 years, the mean age of the recurrence group was 48.2 ± 20.1 years, and the mean age of the nonrecurrence group was 48.5 ± 20.7 years. The age difference between the two groups was not statistically significant ($P = 0.9$).

Out of these patients, 106 patients (8.3%) experienced recurrence, out of whom 59 patients (55.7%) experienced recurrence within 1-2 years, 32 patients (30.2%) within 3-5 years, and 15 patients (14.2%) more than 5 years after successful treatment.

Table 1 shows that the recurrence rate was higher in men than in women (8.7% vs 7.9%) and recurrence in the age group of 15-34 years was higher than the age group of 35-54 years (9.1% vs 7.8%) and the age group of above 55 years (9.1% vs 8.1%) and recurrence in patients with diabetes was higher than in patients without diabetes (9.2% vs 8.2%). But the observed differences were not significant in univariate analysis.

The recurrence rate was higher in the patients with 2+, 3+, or higher sputum smear grading before treatment in comparison to those with 1+ and 1-9 bacilli grading (10.6% vs 4.6%), in patients with positive sputum smear at the end of the second month of treatment in comparison to patients with negative sputum smear at the end of the second month of the treatment (17.9% vs 7.1%), in patients with completed treatment in comparison to cured patients (17.4% vs. 6.8%), and in smokers in comparison to nonsmokers (13.4% vs 7.2%). These differences were statistically significant in univariate analysis [Table 1].

The results of multivariate logistic regression showed that the recurrence rate was more in men than in women and more in diabetic patients than in nondiabetics. The results for the other variables have been shown in Table 2.

Table 1: The distribution of clinical and demographic characteristics of TB patients with relapse and without relapse

Variables	*n*	*n* (%)		*P* (χ^2 test)
		Relapse	Without relapse	
Total	1,271	106 (8.3)	1,165 (91.7)	-
Gender				
Male	714	62 (8.7)	652 (91.3)	0.34
Female	557	44 (7.9)	513 (92.1)	
Age group				
15-34 years	418	38 (9.1)	380 (90.9)	0.78
35-54 years	334	26 (7.8)	308 (92.2)	
≤55 years	519	42 (8.1)	477 (91.9)	
Result of sputum smear before treatment				
1-9 bacilli and 1+	475	22 (4.6)	453 (95.4)	<0.001
2+ and 3+	796	84 (10.6)	712 (89.4)	
Result of sputum smear at the end of 2 months of treatment				
Negative	1,126	80 (7.1)	1,046 (92.9)	<0.001
Positive	145	26 (17.9)	119 (82.1)	
Treatment result				
Cured	1,081	73 (6.8)	1,008 (93.2)	<0.001
Completed treatment	190	33 (17.4)	157 (82.6)	
Diabetes				
No	1,086	89 (8.2)	997 (91.8)	0.37
Yes	185	17 (9.2)	168 (90.8)	
Smoking				
No	1,040	75 (7.2)	965 (92.8)	0.002
Yes	231	31 (13.4)	200 (86.6)	

TB: Tuberculosis

Table 2: Multivariate logistic regression of factors associated with relapse among TB patients

Variables	OR*	CI**	*P*
Gender			
Male	-	-	-
Female	1.2	0.7-1.8	0.52
Age group			
15-34 years	-	-	-
35-54 years	0.7	0.4-1.2	0.21
≤55 years	0.9	0.5-1.4	0.61
Result of sputum smear before treatment			
1-9 bacile and 1+	-	-	-
2+ and 3+	3.2	1.9-5.4	<0.001
Result of sputum smear at the end of 2 months of treatment			
Negative	-	-	-
Positive	2.4	1.4-3.9	0.001
Treatment result			
Cured	-	-	-
Completed treatment	4.2	2.6-6.9	<0.001
Diabetes			
No	-	-	-
Yes	1.1	0.6-2.03	0.72
Smoking			
No	-	-	-
Yes	2.2	1.3-3.7	<0.001

*OR: Odds ratio, **CI: Confidence interval, TB: Tuberculosis

Out of the 102 (8%) cases with smear-positive pulmonary TB and known human immunodeficiency virus (HIV) status, only 12 (0.9%) were HIV-positive. This variable was not used in the analysis due to the unknown HIV status of the majority of patients who entered the cohort.

DISCUSSION

This study has determined the recurrence rate of smear-positive pulmonary TB patients and some of its effective factors. In this study, 8.3% of cases of smear-positive pulmonary TB cases experienced recurrence and over half of the recurrent cases emerged within 1 year or 2 years after successful treatment. The recurrence rate was more in males, those in the age group of 15-34 years, diabetic patients, smokers, patients with 2+ or 3+ sputum smear grading before treatment, patients with positive sputum smear at the end of the second month of treatment, and patients with completed treatment (not cured).

In a study in Cape Town, Western Cape, South Africa that was conducted in order to investigate the recurrence rate of TB in patients after treatment, it was found that out of 612 patients, 18% experienced recurrence.[16] The recurrence rate in the abovementioned study was higher than the present cohort. One of the reasons for the higher recurrence is the higher incidence of smear-positive pulmonary TB in Cape Town (300 per 100,000 persons) in comparison to 4.3 cases per 100,000 persons in the north of Iran.[13,16]

Another study carried out in Karakalpakstan in Uzbekistan on 118 pulmonary TB patients showed that 42 (36%) experienced relapse of TB and the relapse rate in cured patients was 31% and in the group that completed treatment it was 47%.[17] In a retrospective cohort study carried out in Vietnam, 1,068 smear-positive pulmonary TB patients were followed up over an 18-month period and 23 (2.1%) of them experienced relapse.[18] The reported recurrence rate is lower than in the present study and the reason for this difference is likely related to the follow-up period that was shorter than in the reported studies.

In a study carried out in Yemen on 774 smear-positive pulmonary TB patients, the recurrence rate was in 5.7% or 44 cases that was more than in the present study. Multivariate logistic regression showed that smoking and the existence of cavity and diabetes were associated with recurrence but age and sex had no significant relation.[19] In a study conducted in India, 458 pulmonary TB patients were studied in 2012. It was reported that 66 (14.5%) patients had diabetes and the recurrence rate in diabetic patients were more than in those without diabetes.[20] Gounder *et al*. indicated that TB patients with diabetes experienced more unfavorable outcomes of treatment compared to those without diabetes and diabetes increases the risk of TB recurrence and death.[21]

Smoking is considered one of the main public health problems and is known as a risk factor for pulmonary TB. In a study, 2,025 pulmonary TB patients (69.3% smokers and 30.3% nonsmokers) were investigated. The recurrence rate of TB in smokers was more than in nonsmokers (5% vs. 1%) and this result is consistent with the findings of the present study.[22]

One of the limitations of this study was that drug sensitivity test for the detection of drug resistance was not carried out. Additionally, we were not able to separate reinfection from recurrence. But it should be mentioned that about 86% of the recurrent cases experienced a relapse during 1-5 years after successful treatment. Another limitation of the present study was that it did not investigate the relationship between incidence of recurrence and coinfection with HIV.

This study showed that a significant percentage of smear-positive pulmonary TB patients experienced recurrence of TB after successful treatment. Also, the strongest predictors of recurrence were smoking, 2+ and 3+ sputum smear grading before treatment, positive sputum smear at the end of the second month of the treatment, and completed treatment.

According to results of the present study, it is recommended that the sputum smear of all smear-positive pulmonary TB patients should be investigated at the end of the treatment period in order to ensure cure of the patients. Also, there is a need to implement the directly observed treatment, short-course (DOTS) in TB patients more effectively by choosing motivated and committed supervisors from the health personnel. Also, cases in whom the result of

sputum smear was positive at the end of the second month of treatment, an antibiogram of anti-TB drugs should be done in order to apply appropriate remedial procedures as soon as possible.

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